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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
1634	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/642,034	MACK ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-30 and 32-49* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 8-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence search results* .

DETAILED ACTION

1. This application has been transferred from Examiner Holly Schnizer in Art Unit 1653 to Examiner Diana Johannsen in Art Unit 1634.

2. The Amendment filed May 10, 2002, paper no. 9, and the Amendment filed September 16, 2002, paper no. 11, have been entered. Claims 7 and 31 have been canceled, and claims 32-49 have been added. Claims 1-6, 8-30, and 32-49 are now pending.

The paper and computer readable forms of the Sequence Listing filed September 16, 2002, have been entered.

Priority

3. It is noted that Applicant has claimed foreign priority benefits under 35 USC 119 of application no. PCT/US00/06952, filed March 15, 2000. However, this priority claim is improper, as PCT/US00/06952 was filed in the United States, not in a foreign country. See 35 USC 119 and *MPEP* 201.13. Applicant is also referred to *MPEP* 1895 for information regarding priority claims to a PCT application designating the United States under 35 USC 120.

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

It is noted that while Applicant indicated in the transmittal letter of August 18, 2000 that the instant application is a continuation-in-part of several other applications, Applicant has not requested entry of an amendment to the first line of the specification. An application data sheet has not been filed in the instant application.

5. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

6. It is noted that the claims under consideration are drawn to methods requiring detection of expression of a gene that is "at least 75% identical to the sequence disclosed in Figure 1 or Figure 2" (see independent claims 32 and 45). The sequences set forth in the instant application in Figure 1 (SEQ ID NO: 1) and Figure 2 (SEQ ID NO: 4) were not disclosed in any of the applications (including PCT/US00/06952) listed in applicants' oath/declaration and in the above-referenced transmittal letter (see paragraph 4). Accordingly, while the amendment to the specification discussed in paragraph 5, above, will be sufficient to perfect applicants' priority claim under 35 USC 120, the instant claims will not be entitled to the filing date of any of the listed

applications. Rather, the effective filing date of the instant claims will remain the filing date of the instant application, i.e., **August 18, 2000** (see *Hunt Co. v Mallinckrodt Chemical Works*, 177 F.2d 583,587, 83 USPQ 277, 281; MPEP 201.11).

Election/Restriction

7. Applicant's election with traverse of Group IV in Paper No. 9 is acknowledged. The traversal is on the following grounds.

First, applicant particularly argues that Groups IV and XVI should be joined. Upon further consideration, Groups IV and XVI have been joined, and the newly added claims drawn to these two groups (claims 32-49) have been examined.

Regarding the remainder of the restriction requirement, Applicant states only that "all of the inventions in the present application can readily be searched without undue burden." This argument is not persuasive. The Election/Restriction of paper no. 5 established that the multiple inventions claimed in the application are distinct and have acquired a separate status in the art because of their recognized divergent subject matter (see p. 4 of paper no. 5). Applicants' response refers to MPEP 808.02 and acknowledges that a showing of separate status in the art is sufficient to establish an undue burden. However, the traversal does not distinctly and specifically point out any supposed errors in the restriction requirement, or provide any arguments with respect to why Applicants believe that a separate status in the art has not been shown. Inventions IV/XVI, I-III, and V-XV are distinct for the reasons given in paper no. 5, and, as indicated in paper no. 5, have acquired a separate status in the art because of their recognized divergent subject matter.

Cancelled 12-30-03

The requirement is still deemed proper and is therefore made FINAL.

8. Claims 1-6 and 8-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Oath/Declaration

9. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it contains a claim for foreign priority benefits under 35 USC 119 to PCT/US00/06952. This priority claim is improper, as PCT/US00/06952 was filed in the United States, not in a foreign country. See 35 USC 119 and *MPEP* 201.13.

Specification

10. The title of the invention is not descriptive of the subject matter of the elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Novel methods of diagnosing breast cancer.

11. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, e.g., page 14). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

12. The use of the trademarks GeneChip™, Teflon™, Oligotex™, and RNeasy® have been noted in this application. These trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 32-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosing breast cancer in a human in which increased expression of SEQ ID NO: 1 or SEQ ID NO: 4 or of another nucleic acid encoding the amino acid sequence of SEQ ID NO: 5, as compared to levels for these sequences in a normal human breast tissue sample, are detected in a breast tissue sample of a human patient, does not reasonably provide enablement for methods of diagnosing or determining the prognosis for breast cancer in any type of "individual" using any type of "sample" in which the expression of any gene "at least 75% identical to" SEQ ID NO: 1 or SEQ ID NO: 4 is determined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 32-44 are drawn to methods of diagnosing breast cancer comprising steps of "determining the expression of a gene at least 75% identical to" SEQ ID NO: 1 or SEQ ID NO: 4 "in a first sample of a first individual" and "comparing the expression of said gene(s) in the first sample to expression of said gene in a second sample; wherein said comparison is used to diagnose breast cancer." (It is noted that applicants' specification discloses that the sequence disclosed in Figure 1 is SEQ ID NO: 1, and that the sequence disclosed in Figure 2 is SEQ ID NO: 4 (see the Descriptions of Figures 1 and 2)). Claims 33-40 further limit the origin of and/or type of sample(s) employed in the method. Claim 41 further requires that "said gene is the gene disclosed in Figure 1 or Figure 2," while claim 42 requires that "said gene encodes BCR4." Claim 43 requires that "said expression is measured using a labeled nucleic acid probe," while claim 44 states that "said expression is measured utilizing a biochip comprising the sequence disclosed in Figure 1 or Figure 2." Claims 45-49 are drawn to

methods "for determining the prognosis of an individual with breast cancer" comprising "determining the expression of a gene at least 75% identical to" SEQ ID NO: 1 or SEQ ID NO: 4 "in a sample, wherein the expression of the gene is used to determine the prognosis of the individual." Claim 46 further requires that "said gene is the sequence disclosed in Figure 1 or Figure 2," while claim 47 requires that "said gene encodes BCR4." Claim 48 requires that "said expression is measured using a labeled nucleic acid probe," while claim 49 states that "said expression is measured utilizing a biochip comprising the sequence disclosed in Figure 1 or Figure 2." It is noted that the instant specification clearly differentiates "expression of a gene" from expression of a protein, and teaches that determination of "gene expression" requires detection of gene transcripts (see, e.g., p. 6, p. 33-34). Accordingly, the claims as written do not encompass methods of protein/polypeptide detection.

The specification discloses two nucleic acid sequences, SEQ ID NO: 1 and SEQ ID NO: 4, that encode a "breast cancer protein," BCR4. SEQ ID NO: 1 is an mRNA molecule (see description of Figure 1), while SEQ ID NO: 4 is a complete open reading frame (see description of Figure 2). The specification further discloses a single preferred amino acid sequence for BCR4, SEQ ID NO: 5 (see description of Figure 3). The specification provides a comparison of expression of BCR4 gene transcripts in several breast cancer tissue samples as compared to a panel of controls including two samples of normal breast tissue (see Example 1 and Figure 4). The data provided by applicants indicates that BCR4 is expressed at higher levels as compared to both breast tissue controls in 32 of 42 breast cancer tissue samples, and that in at least half of

these samples the increase is two fold or greater (see Figure 4). Accordingly, the data provided by the specification indicates that increased expression of transcripts encoding the particular BCR4 amino acid sequence disclosed by applicants (SEQ ID NO: 5) would be one factor that one of skill in the art would reasonably consider in diagnosis of breast cancer in a human patient. However, it is unpredictable as to whether one of skill in the art could use applicants' invention in a manner reasonably commensurate with the instant claims.

First, with the exception of claims 41, 44, 46, and 49, the instant claims are not limited to methods in which transcripts encoding SEQ ID NO: 5 are detected, but rather encompass detection of the expression of any "gene at least 75% identical" to SEQ ID NO: 1 or SEQ ID NO: 4. The specification exemplifies two particular nucleic acid molecules whose expression is associated with breast cancer; each of these molecules encodes the amino acid sequence of SEQ ID NO: 5. However, the instant claims are sufficiently broad so as to encompass the detection of thousands of different polynucleotides, only a small number of which constitute molecules encoding SEQ ID NO: 5. As the specification provides no evidence of an association between breast cancer and the expression of any nucleic acid molecule encoding an amino acid sequence other than SEQ ID NO: 5, it is unpredictable, based on the teachings provided in the specification, as to whether such an association even exists. Further, with regard to claim 45 and claims dependent therefrom, the specification is silent with respect to any association between the expression of any nucleic acid molecule encompassed by the claims and breast cancer prognosis. Lacking guidance from the

specification, one of skill in the art may look to the teachings of the art for guidance and enablement of a claimed invention. In the instant case, the prior art as exemplified by Goddard et al (WO 01/55178 A2 (published August 2, 2001; filed January 25, 2001; effective filing date January 25, 2000)) discloses an association between breast cancer and expression of nucleic acids encoding LIV-1 (see entire reference, especially page 2, lines 24-26; page 5, lines 17-21; Examples 1 and 6; claim 80). It is a property of the preferred LIV-1-encoding nucleic acid disclosed by Goddard et al (SEQ ID NO: 3 of Goddard et al) that it is 79.8% identical to instant SEQ ID NO: 1 and 99.9% identical to instant SEQ ID NO: 4 (see sequence alignments in the Sequence Search results provided herewith). Further, the instant specification acknowledges that SEQ ID NO: 1 and SEQ ID NO: 4 are similar to nucleic acids encoding LIV-1 (see, e.g., the descriptions of Figures 1 and 2). While SEQ ID NO: 1 and SEQ ID NO: 4 encode a slightly different amino acid sequence than that of LIV-1, and are sufficiently different from the nucleic acids of Goddard et al to establish that LIV-1 and BCR4 are different molecules, instant claims 32-40, 43, 45, and 48 are sufficiently broad so as to encompass methods in which nucleic acids encoding LIV-1 are detected. Additionally, the prior art as exemplified by Taylor et al (British Journal of Cancer 80 (Suppl 2):24 (7/1999)) establishes an association between LIV-1 expression and breast cancer prognosis (see entire reference). Accordingly, given the high level of skill of one of skill in the relevant art, the combined teachings of the specification and of the prior art would enable one of skill to practice not only methods of breast cancer detection in which gene transcripts encoding instant SEQ ID NO: 5 are detected, but methods of diagnosing and

determining the prognosis for breast cancer in which molecules encoding LIV-1 are detected. However, molecules encoding SEQ ID NO: 5 and encoding LIV-1 constitute only a fraction of the nucleic acid molecules whose detection is encompassed by the instant claims. With regard to the numerous other polynucleotides encompassed by the claims, it is unpredictable as to whether one of skill in the art could practice applicants' invention. Neither the specification nor the art provide evidence of the existence of nucleic acid molecules "at least 75% identical" to SEQ ID NO: 1 or SEQ ID NO: 4 that encode polypeptides other than SEQ ID NO: 5 or LIV-1 that are associated with breast cancer. Further, neither the specification nor the art provide evidence of the existence of nucleic acid molecules "at least 75% identical" to SEQ ID NO: 1 or SEQ ID NO: 4 that encode polypeptides other than LIV-1 whose expression is associated with the prognosis of an individual with breast cancer. As it is unknown as to whether any such molecules even exist, it is further unpredictable as to whether any quantity of experimentation would be sufficient to identify additional polynucleotides that would be useful in Applicants' invention. Accordingly, it would require undue experimentation for one of skill in the art to practice the invention as it is now claimed.

Further, it is noted that the evidence in the specification and in the prior art with respect to an association between expression of nucleic acids encoding SEQ ID NO: 5 and LIV-1 are limited to findings of altered expression in human breast tissue samples. The teachings of the specification and of the art do not establish any association between SEQ ID NO: 5 or LIV-1 and breast cancer in non-human patients. Further, neither the specification nor the art provide evidence that one may diagnose breast

cancer by detecting altered expression in other types of samples (such as blood, urine, saliva, etc.). Given the lack of guidance in the specification and in the art, it is unpredictable as to whether applicants' invention may actually be practiced successfully in non-human patients and/or with biological samples other than breast tissue samples. Further, while one of skill could conduct further experimentation to determine whether the invention could be employed successfully with other sample types or in other types of patients, the outcome of such experimentation cannot be predicted, and it is unknown as to whether any quantity of experimentation would be sufficient to allow one of skill to use applicants' invention on other sample types and/or in other patient types. Thus, while the teachings of the specification would enable one of skill in the art to practice methods of diagnosing breast cancer in a human in which in which increased levels of SEQ ID NO: 1 or SEQ ID NO: 4 or of another gene transcript encoding the amino acid sequence of SEQ ID NO: 5, as compared to levels for these sequences in a normal human breast tissue sample, are detected in a breast tissue sample of a human patient, it would require undue experimentation for one of skill in the art to use applicants' invention in a manner reasonably commensurate with the instant claims.

Regarding claims 34-36 and 38-40, it is noted that while the claims are limited to tissue samples/breast tissue samples, the claims encompass diagnosis of breast cancer in non-human patients and are not limited to nucleic acid molecules encoding SEQ ID NO: 5.

Regarding claims 41, 44, 46, and 49, it is noted that while the claims are limited to SEQ ID NOs 1 and 4, the claims encompass non-human patients and the use of any type of biological sample.

Regarding claims 42 and 47, it is noted that the claims are limited to a gene that "encodes BCR4." However, the claims encompass non-human patients and the use of any type of biological sample. Further, while the specification makes clear that BCR4 is different from LIV-1 (see, e.g., descriptions of Figures 1 and 2), the claims are not limited to molecules encoding instant SEQ ID NO: 5, and the specification also discloses that BCR4 polypeptides of the invention may include molecules that are considered homologous to disclosed sequences (as determined by any of a variety of methods), molecules of longer or shorter length, polypeptides that are "derivative or variant breast cancer proteins as compared to the wild-type sequence," covalently modified molecules, etc. (see pages 22-25). Accordingly, the recitation "BCR4" encompasses, at a minimum, thousands of different molecules, while only a single BCR4 polypeptide is disclosed in the specification. The prior art is silent with respect to "BCR4" polypeptides. As discussed above, the teachings of the specification would enable one of skill in the art to practice methods of diagnosing breast cancer in which nucleic acids encoding SEQ ID NO: 5 are detected. However, with regard to nucleic acids encoding any other "BCR4" polypeptide, it is unpredictable as to whether one of skill in the art could practice applicants' invention. Neither the specification nor the art provide evidence of the existence of nucleic acid molecules encoding BCR4 polypeptides other than SEQ ID NO: 5 that are associated with breast cancer. As it is

unknown as to whether any such molecules even exist, it is further unpredictable as to whether any quantity of experimentation would be sufficient to identify additional polynucleotides that would be useful in Applicants' invention. Accordingly, it would require undue experimentation for one of skill in the art to practice the invention as it is now claimed.

Regarding claims 45-49, and claims 46-47 and 49, in particular, it is again noted that, as discussed above in detail, while the prior art establishes an association between LIV-1 expression and breast cancer prognosis, both the specification and the prior art are silent with respect to an association between expression of nucleic acids encoding SEQ ID NO: 5 (including SEQ ID NO: 1 and SEQ ID NO: 4) or any other "BCR4" polypeptide and breast cancer prognosis.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 32-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-49 are indefinite over the recitation of the language "determining the expression of a gene at least 75% identical to the sequence disclosed in Figure 1 or Figure 2" in claims 32 and 45. First, there is insufficient antecedent basis for the limitation "the expression." Second, as Applicants' dependent claims refer to the "gene" of Figure 1 or 2 (see, e.g., claims 41 and 46), and as the specification teaches that determination of "gene expression" refers to detection of gene transcripts (see, e.g., p.

32-34), it appears the claims are intended to require detection of nucleic acid molecules "at least 75% identical to the sequence disclosed in Figure 1 or Figure 2." However, the specification also teaches that the sequences of Figures 1 and 2 are not genes, but rather an mRNA sequence (Figure 1) and an open reading frame (Figure 2) (see descriptions of Figures 1-2). Accordingly, the language "determining the expression of a gene at least 75% identical to the sequence disclosed in Figure 1 or Figure 2" is unclear, as it appears that the terminology "gene" is being used to describe molecules that are not disclosed as actually being genes (but rather gene transcripts). Clarification is required.

Claims 32-44 are indefinite over the recitation of the limitation "the expression of said gene(s)" in claim 32. There is insufficient antecedent basis for this limitation in the claims, as the claim does not previously refer to expression of multiple genes.

Claims 32-44 are indefinite over the recitation of the language "said comparison is used to diagnose breast cancer." This language does not apprise one of skill in the art as to how the "comparing" of step b) allows one to diagnose breast cancer. Thus, while the claims are drawn to a method "of diagnosing breast cancer," the claims do not indicate how diagnosis is to be accomplished. The claims should be amended so as to provide the actual step or steps necessary to achieve "diagnosing breast cancer."

Claim 41 is indefinite over the recitation of the phrase "said gene is the gene disclosed in Figure 1 or Figure 2." As discussed above, the specification discloses that the sequences depicted in Figures 1 and 2 are an mRNA sequence (Figure 1) and an open reading frame (Figure 2) (see descriptions of Figures 1-2). As the teachings of the

specification do not indicate that these sequences are sequences of genes, the recitation "the gene disclosed in Figure 1 or Figure 2" renders the claim unclear and confusing. Further, there is insufficient antecedent basis for the limitation "the gene disclosed in Figure 1 or Figure 2" in the claims.

Claims 42 and 47 are indefinite over the recitation of the limitation "said gene encodes BCR4." First, as discussed above, the specification discloses that the sequences depicted in Figures 1 and 2 are an mRNA sequence (Figure 1) and an open reading frame (Figure 2) (see descriptions of Figures 1-2). As the teachings of the specification do not indicate that these sequences are sequences of genes, the reference in the claims to "said gene" renders the claims unclear and confusing. Second, while the specification discloses a particular preferred BCR4 polypeptide (SEQ ID NO: 5) and teaches that BCR4 is not LIV-1, as discussed above, the teachings of the specification indicate that the term "BCR4" may encompass numerous molecules homologous to the preferred sequences in the specification, to molecules of longer or shorter length, to derivative/variant molecules, to covalently modified molecules, etc. The specification does not indicate that a molecule must have any particular structural or functional property to be considered a "BCR4" polypeptide, and the term "BCR4" is not an art-recognized term, such that one of skill in the art could rely on the art to provide a clear meaning for this terminology. Accordingly, it is unclear as to how the recitation "BCR4" is intended to further limit the claims. Clarification is required.

Claims 45-49 are indefinite over the recitation of the language "wherein the expression of the gene is used to determine the prognosis of the individual" in claim 45.

This language does not apprise one of skill in the art as to how determining gene expression allows one to determine prognosis. Thus, while the claims are drawn to a method "of determining the prognosis of an individual with breast cancer," the claims do not indicate how the prognosis is to be determined. The claims should be amended so as to provide the actual step or steps necessary to achieve determination of prognosis.

Claim 46 is indefinite over the recitation of the phrase "said gene is the sequence disclosed in Figure 1 or Figure 2." As discussed above, the specification discloses that the sequences depicted in Figures 1 and 2 are an mRNA sequence (Figure 1) and an open reading frame (Figure 2) (see descriptions of Figures 1-2). As the teachings of the specification do not indicate that these sequences are sequences of genes, the recitation "said gene is the sequence disclosed in Figure 1 or Figure 2" renders the claim unclear and confusing.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claims 32-40 and 43 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Goddard et al (WO 01/55178 A2 (published August 2, 2001; filed January 25, 2001; effective filing date January 25, 2000)).

Regarding the effective filing date of WO 01/55178 A2, it is noted that WO 01/55178 A2 claims the benefit of U.S. provisional application 60/177,951, and that the subject matter used to make the instant rejection is supported by U.S. provisional application 60/177,951, filed January 25, 2000. It is also noted that applicants' specification discloses that the sequence disclosed in Figure 1 is SEQ ID NO: 1, and that the sequence disclosed in Figure 2 is SEQ ID NO: 4 (see the Descriptions of Figures 1 and 2).

Goddard et al disclose methods of diagnosing breast cancer in a mammal comprising steps of detecting expression of a gene encoding LIV-1 in a test sample and a normal control sample, wherein higher expression in the test sample as compared to the control sample is indicative of the presence of a tumor (see entire reference, especially page 2, lines 24-26; page 5, lines 17-21; Examples 1 and 6; claim 80). It is an inherent property of the preferred LIV-1-encoding nucleic acid disclosed by Goddard et al (SEQ ID NO: 3 of Goddard et al) that it is 79.8% identical to instant SEQ ID NO: 1 and 99.9% identical to instant SEQ ID NO: 4 (see sequence alignments in the Sequence Search results provided herewith). It is also noted that the test samples and control samples disclosed by Goddard et al each inherently constitute either a "first" or "second" sample as compared to each other; the designation in the claims of one sample as a "first sample" and another sample as a "second sample" does not limit or alter the properties of the samples employed in the claimed methods.

Regarding claims 33-40, Goddard et al teach comparing test samples of breast tissues and cells from a mammal with control samples of normal breast tissues and

cells (see p. 5, as well as Examples 1, 5 and 6). With further respect to claims 36 and 40, Goddard et al disclose the use in their methods of cancerous tissues (see, e.g., p. 5, lines 30-31; page 46, lines 18, 34, 36; page 83, lines 2-13). With further respect to claims 37-40, Goddard et al disclose the use of tissue microarray panels of both diseased and healthy control tissue samples that include breast tissue samples obtained from a variety of sources (see, Example 5); Goddard et al thereby disclose the use of first and second samples obtained from different individuals. Regarding claim 43, Goddard et al disclose measuring LIV-1 gene expression "using a labeled nucleic acid probe," as required by the claim (see, e.g., page 46, lines 12-13; page 83, lines 7-13).

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 45 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goddard et al (WO 01/55178 A2 (published August 2, 2001; filed January 25, 2001; effective filing date January 25, 2000)) in view of Taylor et al (British Journal of Cancer 80 (Suppl 2):24 (7/1999)).

Regarding the effective filing date of WO 01/55178 A2, it is noted that WO 01/55178 A2 claims the benefit of U.S. provisional application 60/177,951, and that the subject matter used to make the instant rejection is supported by U.S. provisional application 60/177,951, filed January 25, 2000. It is also noted that applicants' specification discloses that the sequence disclosed in Figure 1 is SEQ ID NO: 1, and that the sequence disclosed in Figure 2 is SEQ ID NO: 4 (see the Descriptions of Figures 1 and 2).

Goddard et al disclose methods of diagnosing breast cancer in a mammal comprising steps of detecting expression of a gene encoding LIV-1 in a test sample, wherein higher expression in the test sample as compared to a normal control sample is indicative of the presence of a tumor (see entire reference, especially page 2, lines 24-26; page 5, lines 17-21; Examples 1 and 6; claim 80). It is an inherent property of the preferred LIV-1-encoding nucleic acid disclosed by Goddard et al (SEQ ID NO: 3 of Goddard et al) that it is 79.8% identical to instant SEQ ID NO: 1 and 99.9% identical to instant SEQ ID NO: 4 (see sequence alignments in the Sequence Search results provided herewith). Goddard et al do not disclose methods for determining the

prognosis of an individual with breast cancer comprising detecting LIV-1 expression in a sample, wherein LIV-1 expression is "used to determine the prognosis of the individual," as required by the instant claims. Taylor et al disclose that LIV-1 expression "shows a highly significant association with the spread of breast cancer to the regional lymph nodes" and teach that LIV-1 is "a suitable prognostic marker for lymph node involvement" (see entire abstract). In view of the teachings of Taylor et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Goddard et al so as to have determined the prognosis of an individual with breast cancer by detecting expression of the LIV-1 gene in a sample from the individual. As Taylor et al disclose that LIV-1 expression is known to be a prognostic marker for lymph node metastasis, an ordinary artisan would have been motivated to have made such a modification in order to have determined whether an individual with breast cancer was at an increased risk of experiencing a spread of cancer to regional lymph nodes, for the advantage of rapidly determining breast cancer prognosis. Regarding claim 48, it is noted that Goddard et al disclose measuring LIV-1 gene expression "using a labeled nucleic acid probe," as required by the claim (see, e.g., page 46, lines 12-13; page 83, lines 7-13).

Conclusion

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Sequence search results are cited to show the sequence identity shared between SEQ ID NO: 3 of Goddard et al and instant SEQ ID Nos 1 and 4.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
December 30, 2002